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REVIEW ARTICLE

Review Series: Advances in Consensus, Pathogenesis and Treatment of Urticaria and Angioedema

Guideline for Hereditary Angioedema (HAE) 2010 by the Japanese Association for Complement Research - Secondary Publication

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ABSTRACT
This guideline was provided by the Japanese Association for Complement Research targeting clinicians for making an accurate diagnosis of hereditary angioedema (HAE), and for prompt treatment of the HAE patient in Japan. This is a 2010 year version and will be updated according to any pertinent medical advancements.

KEY WORDS
allergic inflammation, angioedema, complement, guideline, Japan

PURPOSE OF THIS GUIDELINE

This guideline was provided by the Japanese Association for Complement Research targeting clinicians for making an accurate diagnosis of hereditary angioedema (HAE), and for prompt treatment of the HAE patient.

HAE is caused by a deficiency or improper function of the inhibitor of complement component protein C1 (C1-INH), which affects the blood vessels. Patients with HAE can develop rapid swelling of the hands, feet, limbs, face, intestinal tract, larynx or trachea. HAE is relatively easy to diagnose if you are familiar with the disease and it may be treated efficiently. The lack of an accurate diagnosis can have serious consequences. Patients with misdiagnosed HAE may un-

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Table 1 Treatment during an episode

Treatment During an Episode	Laryngeal Edema	Subcutaneous Edema-Excluding Face and Cervical Region	Subcutaneous Edema-Face and Cervical Region	Abdominal Symptoms
Follow-up	-	+	+	+
Tranexamic acid	-	+	+	+
C1-INH	+	+/-	+	+
Intubation in ICU	+	-	-	-

dergo unnecessary medical procedures (e.g. appendectomy, exploratory laparotomy). We all hope that patients suffering from the disease will be immediately diagnosed with HAE and treated appropriately. We will update this guideline according to any pertinent medical advancements.

GENERAL INFORMATION ON HAE

a) Epidemiology: one in every 10,000 to 150,000 people (mostly reported as one in every 50,000).
b) Types of HAE
   i) Type 1, autosomal dominant inheritance (85% of all HAE): Low amount of C1-INH protein and low level of C1-INH activity.
   ii) Type 2, autosomal dominant inheritance (15% of all HAE): Normal or increased amount of C1-INH protein and low level of C1-INH activity.
   iii) Type 3 is very rare and not reported in Japan, occurring mostly in females (estrogen-dependent). Details of the pathogenesis are unknown, and the mutation of coagulation factor XII is detected in some families. Both C1-INH protein and C1-INH activity are normal.
   iv) Sporadic cases not related to family history are observed in approximately 25% of all HAE.

DIAGNOSIS

HAE is often unrecognized or misdiagnosed because it is rare, and its symptoms are similar to many other more common angioedema.

a) Differential diagnosis for HAE: acquired angioedema (AAE), drug-induced angioedema, etc.
b) Symptoms of suspected HAE
   i) Angioedema can be caused in any tissues and its symptoms may vary in each organ.
      • Laryngeal edema - the fatality rate is 30% when not appropriately treated. Rare in children under 3 years old.
      • Subcutaneous edema, submucosal edema (not associated with itching, can be seen all over the body, swelling is sometimes below the surface of the skin).
      • Digestive symptoms (abdominal pain, nausea, vomiting, diarrhea).
   ii) Angioedema attacks may be induced by psychological stress, physical stress such as trauma, tooth extraction, surgical operation, overwork, pregnancy, menstruation, drugs, etc.
   iii) Angioedema usually peak within 24 hours and subside within 72 hours, however, they may continue for more than 72 hours in some cases.
   iv) Approximately 75% of HAE patients have family histories.
   v) Attacks can occur in all ages.
c) Laboratory serum test
   C1-INH activity is low in all HAE patients. Therefore, C1-INH activity is the most important measurement for the diagnosis of HAE and this test is covered by health insurance in Japan. During an angioedema episode, the level of complement component C4 decreases in 98% of HAE patients, and therefore may be a good marker for the diagnosis of HAE during its episode.
d) Determination of HAE types
   To determine the type of HAE, quantification of C1-INH protein is required, although the cost is not covered by Japanese health insurance.
      • Low C1-INH protein - Type 1 HAE
      • Normal C1-INH protein - Type 2 HAE
e) When there is no family history, diagnosis should be differentiated from AAE. When the level of C1q (not covered by the Japanese health insurance) is low, it can generally be diagnosed as AAE. However, in rare cases, low levels of C1q can be detected in HAE and genetic analysis is required for accurate diagnosis.
f) When Type 3 HAE is suspected, a mutation of Factor XII may be identified.

TREATMENT DURING AN EPISODE (Table 1)

a) Laryngeal edema
   i) C1-INH replacement therapy (for less than 50 kg, 500 units and for more than 50 kg, 1,000 to 1,500 units, intravenous injection).
   ii) Intra-tracheal intubation or tracheotomy in Intensive Care Unit for respiratory distress by airway stenosis.
b) Subcutaneous edema (excluding face and cervical region)
   i) Follow-up first.
   ii) If no improvement is seen, give the following treatment: Tranexamic acid 15 mg/kg every 4

hours. For severe cases in which symptoms do not improve by tranexamic acid treatment alone, C1-INH replacement therapy is required (for less than 50 kg, 500 units and for more than 50 kg, 1,000 to 1,500 units, intravenous injection).

c) Subcutaneous edema (face and cervical region)
   i) Tranexamic acid (15 mg/kg every 4 hours).
   ii) C1-INH replacement therapy (for less than 50 kg, 500 units and for more than 50 kg, 1,000 to 1,500 units, intravenous injection).
d) Abdominal symptoms
   i) Tranexamic acid (15 mg/kg every 4 hours).
   ii) C1-INH replacement therapy (for less than 50 kg, 500 units and for more than 50 kg, 1,000 to 1,500 units, intravenous injection).

SHORT-TERM PROPHYLAXIS

a) Cases with minimal stress: dental treatment (less invasive), etc. Treatment for prevention is not required, but C1-INH replacement should be ready for use.
b) Cases with intensive stress: highly invasive dental treatment, surgical operations, etc. Give C1-INH replacement therapy (for less than 50 kg, 500 units, and for more than 50 kg, 1,000 to 1,500 units, intravenous injection) an hour prior to the operation. Furthermore, a second C1-INH replacement therapy should be prepared.

LONG-TERM PROPHYLAXIS

The following treatment is recommended for patients with a history of laryngeal edema, those who develop symptoms once or more a month, and/or suffered from symptoms for more than 5 days a month.

a) Tranexamic acid
   i) 30-50 mg/kg/day administered in divided doses 2-3 times a day.
   ii) Adverse reactions: muscle ache, muscle weakness, fatigue, and reduction in blood pressure.
b) Danazol
   i) 2.5 mg/kg/day(maximum 200 mg/day) will be administered for one month, if it is not effective, 300 mg/day will be administered for one month, and if it is still not effective, 400 mg/day will be administered for one month. If 200 mg/day is effective, 100 mg/day will subsequently be administered for one month and the amount will be reduced to 50 mg/day or 100 mg/every second day.
   ii) Contraindication: children, pregnant women, lactating women, and cancer patients.
   iii) Adverse reactions: virilization, hepatic disorder, hypertension, lipid abnormality, polycythemia, and hemorrhagic cystitis.
   iv) Follow-up: Blood testing is required every 6 months. For patients treated with more than 200 mg/day Danazol, an abdominal ultrasonography is required every 6 months and for cases treated with less than 200 mg/day an abdominal ultrasonography is required every year, due to a possibility of hepatic tumorigenesis.

REFERENCE MATTERS FOR DIAGNOSIS

a) For the initial screening for HAE, a serum C4 measurement during attacks should be considered.
   i) Low C4 level → Conduct C1-INH activity measurement.
   ii) Normal C4 level → HAE can basically be ruled out.
b) Measurement of the C1-INH activity is essential for making an accurate diagnosis of HAE
   i) Low C1-INH level → It can be diagnosed with angioedema caused by a deficiency of C1-INH. Differentiate the types as follows.
      • With a family history → It can be diagnosed as HAE. → Conduct quantitation of C1-INH. → If the level is low, it can be diagnosed as Type 1, and if the level is normal or increased, it can be diagnosed as Type 2.
      • No family history → Conduct serum C1q measurement and if the level is low, it can be diagnosed as AAE. However, it should be taken into account that low C1q can occur in some HAE patients. → A genetic analysis is desired in order to make an accurate diagnosis.
   ii) Normal C1-INH level → Suspect of Type 3 or drug-induced angioedema. → Confirm his/her medication history (especially, antihypertensive drugs, estrogen preparations). In addition, Type 3 has not been reported in Japanese; however, according to reports in Caucasians, it is related to family history and occurs mostly in women.

NOTES

Please contact us if you have any opinions about this guideline. Contact: Takahiko Horiuchi, Steering Committee, The Japanese Association for Complement Research. E-mail: horiuchi@intmed1.med.kyushu-u.ac.jp.

Please refer to our website at http://square.umin.ac.jp/compl/ if you have any concerns about C1-INH activity measurement, protein quantitation, and genetic analysis.

C1-INH formulation is provided as Berinert P (trade name) (CSL Behring) in Japan. Information on hereditary angioedema can be obtained from homepage of CSL Behring at http://www.cslbehring.co.jp, or a dedicated website for hereditary angioedema "HAE Information Center" at http://www.hae-info.jp. For example, you can find information like "Tranexamic acid is provided as Transamin (trade name)

(Daiichi Sankyo), etc.", and "Danazol is provided as Bonzol (trade name) (Mitsubishi Tanabe Pharma), etc.".

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